IPEC Americas & IQ Consortium - FDA meeting to discuss Novel Excipients Initiative
June 4, 2015

Attendees

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Meeting Summary

After introductions, the representatives from IPEC-Americas and the IQ Consortium (IPEC/IQ) briefly described their organizations and members. IPEC-Americas represents makers, users (innovators, generics, OTCs) and distributors of pharmaceutical excipients. The IQ Consortium represents many of the major innovator pharmaceutical companies. Both organizations have a significant interest in facilitating the use of novel (new) excipients to improve drug product quality, manufacturability and performance.

The intent of this meeting was not to make decisions, but rather to initiate a dialog between the Agency and Industry about the development of an appropriate mechanism for the independent safety evaluation of novel excipients that would meet the requirements of all parties.

A backgrounder document was provided to all attendees prior to the meeting which summarized the need for such a mechanism and to provide basic information concerning the concepts that IPEC/IQ have envisioned.

1. Meeting purpose

The purpose of this meeting was to allow members of IPEC/IQ an opportunity to present information related to the reasons why the current system of having all types of novel excipients only reviewed as part of a drug application does not facilitate the use of these novel excipients and to present concepts for possible alternatives.

Prior to the meeting, attendees were provided with a backgrounder document which included concept proposals to develop a user fee program to support the independent review and qualification of excipient safety information contained in Type IV or V Drug Master Files (DMFs) with the goal of encouraging use of novel excipients by Drug Application sponsors. This pharm/toxicology review of the DMF would be an independent assessment outside of the drug approval process and would take place prior to submission of a drug application containing the excipient in a formulation.

2. Presentation by IPEC Americas/IQ Consortium (refer to Appendix A for slides)

This presentation provided the current situation for novel excipient development, adoption and approval as well as challenged whether this is the most appropriate model to advance future innovation in drug development. Information was presented to substantiate various issues and describe how the existing approach is having negative effects on the development of novel excipients and consequent impact on efficiency and effectiveness of drug development and other innovation areas such as advanced manufacturing methods to produce quality drug products. IPEC/IQ highlighted the fact that excipient manufacturers currently have little incentive to develop anything that would be defined as a novel excipient to help pharmaceutical companies resolve formulation problems or move towards advanced manufacturing methods. Those who have developed novel excipients in the past are deciding to no longer support these investments since the time to acceptance in the market is very long and uncertain.

Towards the end of the presentation, IPEC/IQ presented several options to provide potential solutions to improve development and adoption of novel excipients and the regulatory process for such materials. Throughout this document these ideas will be referred to as “concepts”.

The presentation explored the following concepts:

- An FDA Independent Safety Assessment of novel excipients is needed outside of a drug application – sponsor would indicate intended types of use & levels
    - IPEC/IQ is not looking for an approval of the excipient but rather a way to have the safety of the excipient evaluated and qualified for potential use in a particular route of administration and exposure level.
    - This type of system would give drug developers greater confidence to include novel excipients in drug products and facilitate innovation.
- Novel excipient safety information, including studies and related information, could be provided in Type IV or V DMFs.
- A GDUFA/PDUFA type user fee system could provide resources to FDA to perform these independent safety assessments or qualifications.
- Publication of a list of excipients, evaluated by an FDA independent safety assessment that could be considered "qualified" for specific intended uses and levels in pharmaceutical products.

IPEC/IQ requested initial feedback from the FDA representatives at the meeting concerning the concept proposals so that they could consider the feedback and address FDA's concerns.

3. Key questions and discussion points for consideration

- Karen Davis Bruno recommended that IPEC-Americas and the IQ Consortium investigate the FDA's Biomarker Qualification Program to see how the concepts involved with this program might apply to what is desired for the qualification of novel excipients.
    - IPEC/IQ was not familiar with this program and felt that this was a good recommendation for follow up. IPEC/IQ will evaluate similarities in this program with what is needed for novel excipients and determine how they might be able to leverage this information for use with the novel excipient concepts.
- FDA stated that the ultimate approval of a novel excipient would need to consider the "Context of Use" in a drug product.
    - IPEC/IQ re-stated that their concept proposal did not expect that the excipient would be "approved" outside of the drug approval process but explained that there is a real need for some type of preliminary safety assessment or qualification on the excipient itself for general intended routes of administration and use levels in parallel to industry efforts to advance these novel excipients in a drug product.
- FDA had questions regarding the type and level of toxicology data which would be available for such an independent safety assessment since many older Type IV DMFs only have limited data available.
    - IPEC/IQ explained that the safety data which would typically be contained in a Type IV or V DMF for a novel excipient (including existing excipients being used at a higher level of use or in a different route of administration and co-processed excipients) would need to be robust and meet current expectations if the novel excipient was to be submitted to FDA for this qualification process.
- FDA mentioned that the CMC information in a Type IV DMF cannot be separated from an assessment of the toxicology data to do an appropriate evaluation.

- IPEC/IQ totally agreed with this statement and said they would expect that this would be part of whatever system we can co-develop with FDA for a science and risk-based assessment of the safety of a novel excipient.

- FDA recommended that IPEC/IQ develop ideas for how the logistics would realistically work for a user fee type of system given that the same novel excipient could potentially be made by multiple suppliers.
  - IPEC/IQ stated that they would include this issue in their ongoing discussions to develop further details for the concept proposal after meeting with FDA.
- Some FDA representatives asked for additional information to understand why pharmaceutical companies cannot use the existing system to have novel excipients assessed during the regular drug approval process and why this was seen as having too much risk.
  - IPEC/IQ provided additional comments regarding the level of risk that a pharmaceutical company is willing to take to use a novel excipient in a new drug application when there is uncertainty as to FDA's thinking about the safety data that exists for that novel excipient.
  - In the future the existing system will no longer be able to sustain entry of novel excipients that have the potential to address key challenges (such as drug solubility/permeability issues) and opportunities (such as continuous manufacturing) in the pharmaceutical industry. Without an approved pathway for an independent novel excipient qualification process, it is feared that very few novel excipients will be developed just as the need for these materials becomes increasingly important.

4. Next Steps

IPEC/IQ requests a follow up meeting to share additional information and collaborate towards a workable solution to facilitate the development and use of novel excipients.

Susan Zuk indicated that after the presentation from IPEC/IQ, a briefing will be prepared for Janet Woodcock so that the concept proposal can be considered by the Center.

Appendix A
Presentation from IPEC/IQ

IQ & IPEC-Americas Novel Excipients Initiative

Presentation to U.S. Food and Drug Administration
June 4, 2015

Our Organizations

- International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) http://iqconsortium.org
  - Technically-focused organization of industrial pharmaceutical and biotechnology companies with a mission of advancing science-based standards and regulations for pharmaceutical and biotechnology products worldwide
- International Pharmaceutical Excipients Council (IPEC-America) http://ipecamericas.org/
  - Industry association that develops, implements, and promotes global use of appropriate quality, safety, and functionality standards for pharmaceutical excipients and delivery systems

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Novel Excipient

A material or a composition that has not been previously used in an approved drug product in the US (i.e. not listed in FDA Inactive Ingredient Database (IID)) or that has been previously used in an approved drug product but which it is desired to employ for a new route of administration, or a higher level of use than has been previously listed in the IID. A novel excipient can also be defined as a new co-processed excipient made from two or more previously approved excipients.

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Role of Novel Excipients in Pharmaceutical Innovation

- **Extending product options**
  - Greater choice for patient/provider
  - Different routes of administration
- **Improving manufacturing processes across the industry**
  - Increasing robustness and efficiency of traditional processing
  - Alternative manufacturing concepts
  - Continuous manufacturing
- **Enabling new therapeutic entities (NCEs/NBEs) for patients**
  - Accelerating next-generation therapeutics through pipelines
  - Solving drug delivery issues (improving bioavailability, stability)
  - Patient-centric products (e.g. pediatric formulation, long duration)
  - Cost-effective product innovations (hospital - home administration)
  - "Making products possible" – essential to success of NCE/NBE

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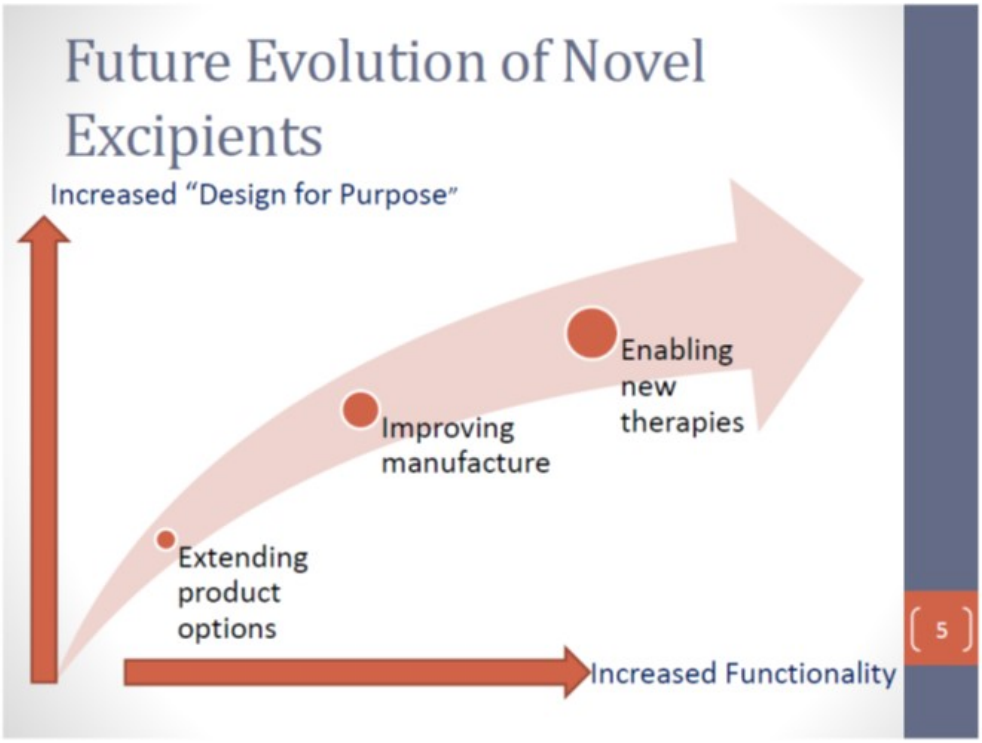
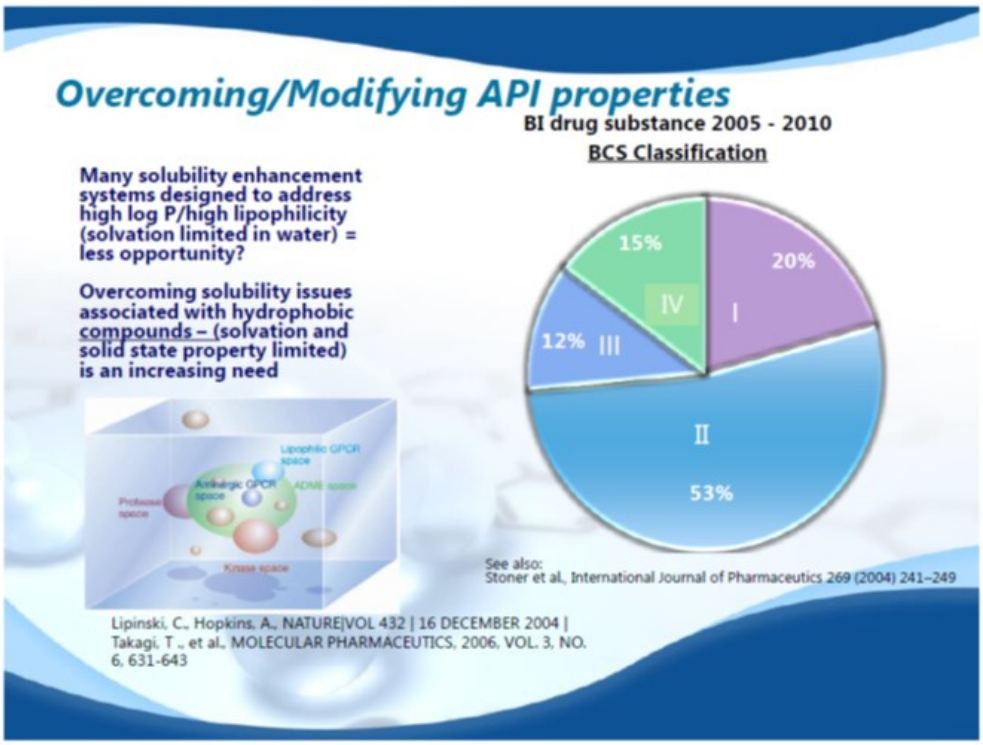

Future Evolution of Novel Excipients
Increased "Design for Purpose"
Enabling new therapies
Improving manufacture
Extending product options
Increased Functionality
5


Overcoming/Modifying API properties
BI drug substance 2005 - 2010
BCS Classification
Many solubility enhancement systems designed to address high log P/high lipophilicity (solvation limited in water) = less opportunity?
Overcoming solubility issues associated with hydrophobic compounds – (solvation and solid state property limited) is an increasing need
15%
20%
IV
I
12%
III
II
53%
See also:
Stoner et al., International Journal of Pharmaceutics 269 (2004) 241–249
Lipinski, C., Hopkins, A., NATURE|VOL 432 | 16 DECEMBER 2004 |
Takagi, T., et al., MOLECULAR PHARMACEUTICS, 2006, VOL. 3, NO. 6, 631-643

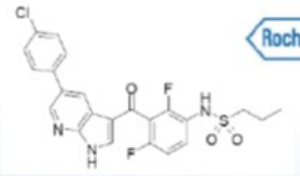
What's the point in investing in new excipients?

Wagle, N., et al, J.Clin. Oncol., 2011, 29, 3085-3096

Enabling products for patients

Excipients Enabling New Products for Patients

(excerpts from the CHMP Assessment Report, 15th Dec 2011)



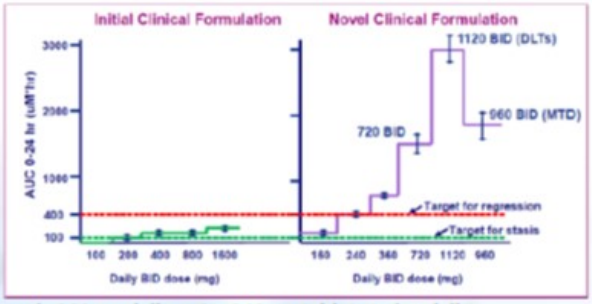
Roche

Zelboraf vemurafenib

- Vemurafenib is a BCS Class IV compound
- Crystalline vemurafenib (Form II) is non-hygroscopic powder with a Mpt of ~ 271°C.
- Solubility in water is very low (<0.0001 mg/ml); not appreciably soluble in many common organic solvents
- First clinical trial was conducted on a capsule formulation with 100 mg and 300 mg micronized crystalline Form I of vemurafenib.
- Form I of vemurafenib gradually transformed to Form II and the bioavailability observed was low.

Impact

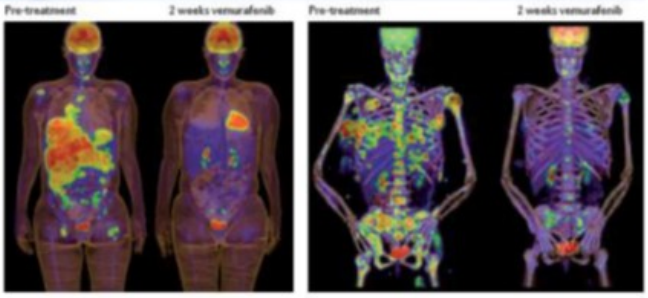
Delivering An Important Treatment to Patients



Puzanov *et al*, ASCO, 2009

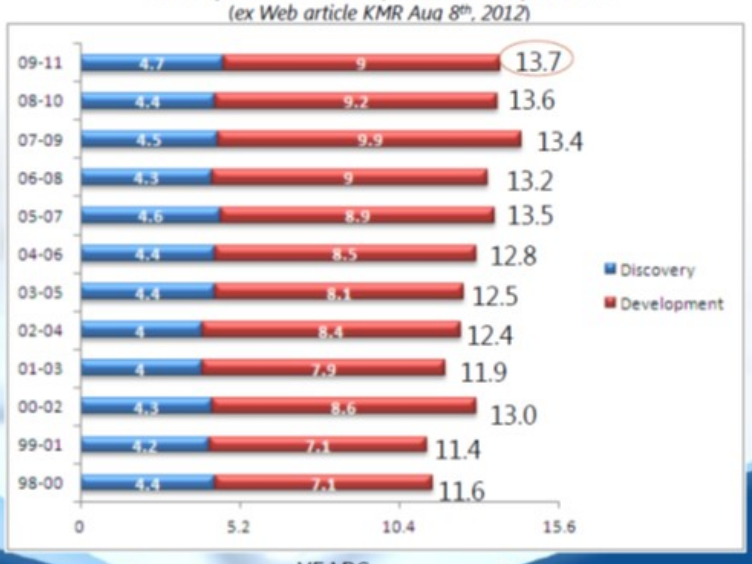
Dose is 960mg daily = 4 x 240mg tablets twice daily

BOLLAG, G et al, NATURE REVIEWS | **DRUG DISCOVERY** VOLUME 11 | NOVEMBER 2012 | **873**



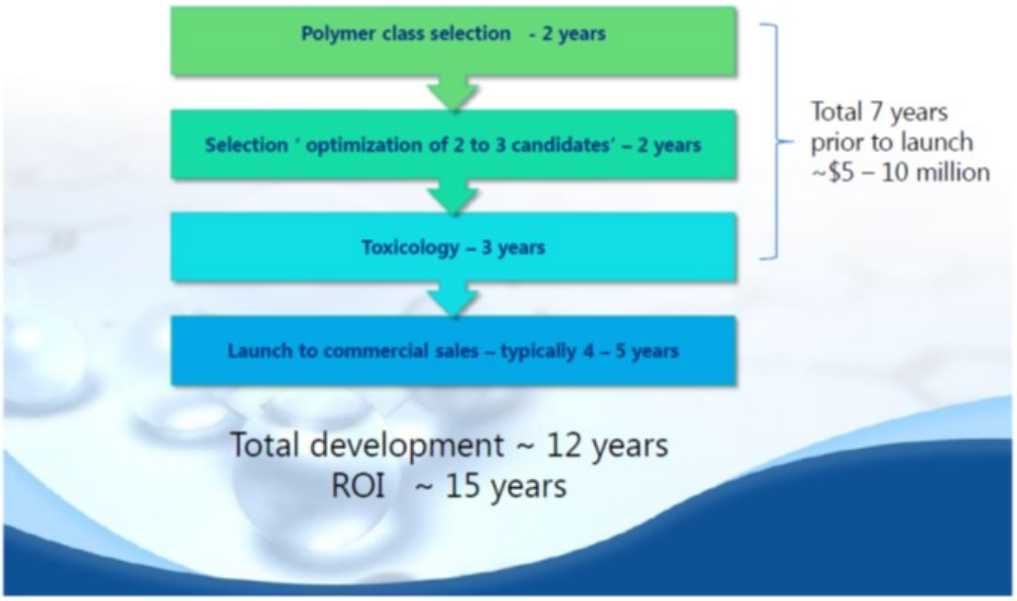
Pharma R & D Cycle Time

NME Cycle Time – Composite Industry Median
(ex Web article KMR Aug 8th, 2012)

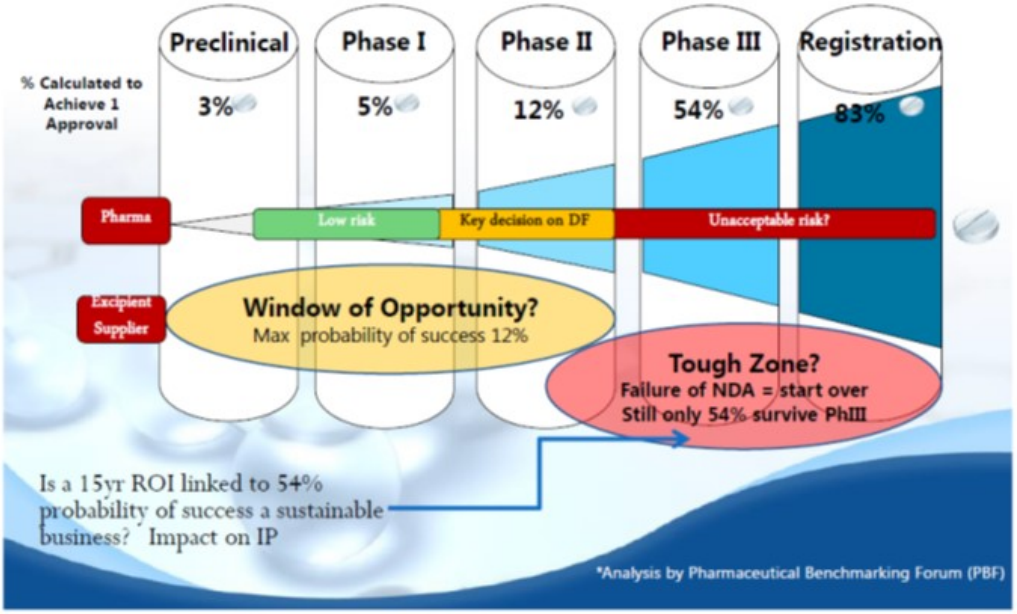


R&D CT	
Years	% Change
09-11	1%
08-10	1%
07-09	1%
06-08	-2%
05-07	8%
04-06	3%
03-05	1%
02-04	1%
01-03	-6%
00-02	14%
99-01	-2%
98-00	-

Novel Excipient Development



New Excipient Risks and Challenges



Unmet Needs: IQ Survey Results

- ~2/3 of responding companies interested in novel excipients
- Oral delivery>>Sub cutaneous >Intravenous >>inhalation & transdermal >> intra-articular & intra-vitreal delivery
- Examples of areas of interest:
  - Need increase in number of approved hydrophilic solvents for oral use
  - Enhanced oral absorption of peptides and proteins
  - Solubilizers for i.m., s.c. and i.v. use
  - Permeability enhancers
  - More excipients for inhalation
  - Protein aggregation prevention
  - Peptide and protein stability

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IQ Interest in Novel Excipients

- Drug Product and Preclinical Safety Working Group Joint Initiative on use of excipients in early safety programs
  - Survey completed and review document in preparation
  - Future developments
    - Generate "target product profiles" for novel excipients
    - "Compound libraries" for evaluating novel excipients?
    - Creation of pharma "consensus-based" pre-clinical safety assessment programs for novel excipients (leveraging existing regulatory/NEEC procedures
    - Linkage to other IQ initiatives with excipient interests (e.g., pediatric formulation)
- **IPEC/IQ collaboration to improve approval and adoption of novel excipients**

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Modernized Review Pathway Needed

- Current process presents major challenges to innovation
  - High investment to develop novel excipient
  - Regulatory approval framework constrains use
    - Pharmaceutical industry reticence to use novel excipients
    - Uncertainty about data required during regulatory review process
- New pathway could address challenges to innovation
  - It would facilitate increased investment in development and in use of novel excipients
  - This would have noteworthy benefits for patients

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Modernizing Review of Novel Excipients

- Points for consideration/discussion:
  - FDA Independent Safety Assessment of novel excipients outside of a drug application – sponsor would indicate intended types of use & levels
    - *Would give drug developers greater confidence to include novel excipients in drug products*
  - Use of Type IV or V DMFs for submission of inactive ingredient safety information including studies and bridging arguments
  - Potential value of a GDUFA/PDUFA type user fee system which could provide resources to FDA for these independent safety assessments
  - Publication of a list of excipients which have undergone the FDA's independent assessment and are considered to be "endorsed" by FDA for specific intended uses in pharmaceuticals
    - Other similar programs: FDA GRAS Notification, FEMA GRAS, CIR

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Next steps

- Follow up meeting to provide additional data and collaborate on future solutions

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Thank You

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